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Effects of Weight-Loss Medications on Cardiometabolic Risk Profiles: A Systematic Review and Network Meta-analysis

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BACKGROUND & AIMS: We performed a systematic review and network meta-analysis to evaluate the overall and comparative effects of weight-loss medications approved by the Food and Drug Administration for long-term use on cardiometabolic risk profiles of obese adults. **METHODS:** We performed a systematic literature review through February 28, 2017 to identify randomized clinical trials of the effects of Food and Drug Administration–approved weight-loss medications (ie, orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide) administered to obese adults for 1 year or more, compared with placebo or another active agent. Outcomes of interest included changes in blood glucose (fasting blood glucose [FBG] and hemoglobin A1c), cholesterol profile (low-density lipoprotein and high-density lipoproteins), blood pressure (BP; systolic/diastolic), and waist circumference (WC). We performed pair-wise and network meta-analyses with outcomes reported as weighted and standardized mean differences. Quality of evidence was rated using GRADE (Grading of Recommendations Assessment, Development and Evaluation). **RESULTS:** In a meta-analysis of 28 randomized controlled trials (29,018 participants; median body mass index, 36.1 kg/m^2), we associated weight-loss medications with a modest decrease in FBG (weighted mean difference, 4.0 mg/dL; 95% confidence interval, −4.4 to −3.6 mg/dL) and WC (weighted mean difference, reduction of 3.3 cm; 95% confidence interval, −3.5 to −3.1 cm), without clinically meaningful changes in systolic/diastolic BP or cholesterol profile vs placebo (standardized mean difference <0.2); effects varied among drugs. Phentermine-topiramate use was associated with a substantial decrease in WC and a modest decrease in FBG, hemoglobin A1c, and BP, and had minimal effect on cholesterol. Liraglutide use was associated with a substantial decrease in FBG, hemoglobin A1c, and WC, and a minimal effect on BP and cholesterol. Naltrexone-bupropion use was associated with moderate increase in high-density lipoprotein cholesterol, but had a minimal effect on FBG and WC. Orlistat use was associated with a decrease in low-density lipoprotein and high-density lipoprotein cholesterol. No drug improved all cardiometabolic risk factors. **CONCLUSIONS:** In a systematic review and network meta-analysis, we found Food and Drug Administration–approved weight-loss medications to have only modest positive effects on cardiometabolic risk profile. Further research is needed to evaluate the long-term cardiometabolic benefits of these medications. PROSPERO: CRD42016039486.

Keywords: BMI; Heart Disease; Vascular; Pharmacotherapy.

Obesity is associated with an unfavorable cardiometabolic risk factor profile,[1] which portends an excess risk of cardiovascular morbidity and mortality. Lifestyle interventions have only been modestly effective in alleviating this excess risk.[2] Pharmacologic therapies for obesity are promising, with varying efficacy for weight loss.[3] The average weight loss with the 5 agents approved for long-term management of obesity by the US Food and Drug Administration (FDA)—orlistat, lorcaserin, naltrexone-bupropion, liraglutide, and phentermine-topiramate—ranges from 2.6 to 8.8 kg over placebo, with approximately 20%–54% patients achieving ≥10% weight loss after 1 year of therapy.[3] However, whether therapeutic effectiveness of weight-loss therapies translates to improvement in cardiometabolic profile is unknown. Dedicated randomized trials examining cardiovascular outcomes with a few weight-loss agents have either been stopped prematurely or were designed to assess cardiovascular safety for non–weight-loss indications.[4,5] Moreover, few trials have compared these drugs with each other. While important for clinical decision making, little is known about the overall and comparative effects of these medications on cardiometabolic risk factors.

To address this knowledge gap, we conducted a systematic review and network meta-analysis assessing the effect of long-term pharmacotherapy for weight loss on various facets of cardiometabolic risk, including blood glucose, cholesterol profile, blood pressure (BP), and visceral adiposity.

***Authors share co-first authorship.**

Abbreviations used in this paper: **BMI, body mass index; BP, blood pressure; CI, confidence interval; FBG, fasting blood glucose; FDA, Food and Drug Administration; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; RCT, randomized controlled trial; SMD, standardized mean difference; WC, waist circumference; WMD, weighted mean difference.**

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Several pharmacological weight loss agents have been approved. However, whether therapeutic effectiveness of weight loss therapies translates to improvement in cardiometabolic profile is unknown.

NEW FINDINGS

FDA-approved pharmacological agents for long-term treatment of obesity have modest impact on modifying key cardiometabolic risk factors. Most drugs were associated with improvements in waist circumference, but only marginal improvements in serum cholesterol profile and BP.

LIMITATIONS

There are limited head-to-head trials, which limits inference on comparative efficacy of different agents.

IMPACT

Given the modest effects of pharmacological weight loss medications on cardiometabolic risk profile even after a year of drug therapy, detailed research into long-term effect of these medications on cardiovascular risk is warranted.

Methods

Study Selection, Data Abstraction, and Risk of Bias Assessment

The study was conducted using an a priori protocol (PROSPERO #CRD42016039486),[6] and reported in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension statement for network meta-analysis.[6] The search strategy was designed and conducted by an experienced medical librarian (LJP) with input from study investigators, utilizing various databases from inception to February 28, 2017. The databases included Ovid Medline, EMBASE, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials. In addition, we searched clinical trial registries (www.clinicaltrials.gov and www.clinicaltrialsregister.eu), conference proceedings and performed a recursive search of published systematic reviews. Controlled vocabulary supplemented with keywords was used to search for randomized controlled trials (RCTs) of drug therapy for weight loss. Details of the search strategy are shown in the Supplementary Materials and Methods.

In accordance with a previous approach,[3] we selected RCTs in obese (body mass index [BMI] $\geq$30 kg/m^2) or overweight (BMI 25−29.9 kg/m^2) adults (aged >18 years), with and without excess weight-associated comorbidities (hypertension, hyperlipidemia, diabetes mellitus, impaired glucose tolerance, or obstructive sleep apnea); treated with a pharmacologic agent approved for long-term treatment of obesity (orlistat, lorcaserin, naltrexone-bupropion, liraglutide, or phentermine-topiramate) administered at the most effective approved doses for $\geq$1 year; compared against another active agent or placebo; and reporting $\geq$1 prespecified cardiometabolic outcomes besides a primary weight-loss outcome ($\geq$5% of baseline weight loss or mean weight loss in kilograms). We excluded trials of short-term or nonapproved pharmacologic agents (eg, phentermine, rimonabant, and sibutramine); trials in special populations (such as patients with nonalcoholic fatty liver disease or polycystic ovarian syndrome patients); and observational studies. The study selection flowsheet is presented in Figure 1.

Data on study-, patient-, and treatment-related characteristics were abstracted onto a standardized form by at least 2 authors independently. All of our study outcomes are reported on an interval scale and required abstraction of mean change from baseline, the SD of the mean change, and the number of individuals for each study arm. We followed the recommended strategies for calculating SD for mean change when variance estimates were not reported as a SD. Risk of bias for individual studies was assessed using the Cochrane Risk of Bias assessment tool.[7]

Outcomes Assessed

Cardiometabolic risk outcomes were defined a priori, and included glucose profile (fasting blood glucose [FBG; mg/dL] and/or hemoglobin A1c); markers of lipoprotein metabolism (low-density lipoprotein [LDL; mg/dL], high-density lipoprotein [HDL, mg/dL]; systolic and diastolic BP [mm Hg]; and central adiposity, assessed using waist circumference [WC; cm]). High-sensitivity C-reactive protein, serum triglycerides, and markers of insulin resistance (Homeostatic Model Assessment for Insulin Resistance) were considered as potential outcomes in the study protocol, but were inconsistently reported and, therefore, not analyzed.

For meta-analysis, all study outcomes were abstracted as continuous changes from baseline and were obtained at the 1-year follow-up. We used an intention-to-treat approach for all study outcomes. In accordance with FDA's recommendations regarding trials of weight-loss agents,[8] missing values were most consistently imputed using last-observation carried forward imputation across studies, which was, therefore, used in the meta-analysis. In trials with multiple medication doses, the most effective FDA-approved dose was used.

Statistical Analysis

We performed pairwise meta-analyses for all treatment comparisons using a DerSimonian and Laird random effects approach to obtain pooled effect estimates for all pairwise drug comparisons. Because all study outcomes were on a continuous scale, we reported the pooled estimates as both weighted mean difference (WMD) and standardized mean difference (SMD), along with their respective 95% confidence intervals (CI). We examined for statistical heterogeneity using the I^2 statistic,[9] and assessed small-study effects, including publication bias, by examining funnel plot asymmetry and Egger's regression test.[8,10]

Next, we conducted a network meta-analysis for each study outcome incorporating data from all studies in a random-effects model. Similar to methods we have described previously,[11] we constructed a "consistency" model that accounts for heterogeneity in study effect across trials, but assumes that the drug effects are not systematically different across trials.[12] In this model, while direct and indirect estimates for a comparison between 2 agents (A and B) may differ across studies due to heterogeneity, these differences do not represent systematic differences as a function of trial design, that is, the estimate for comparing agents A and B from 2-arm trials comparing A and B are similar to those derived from 3-arm trials (A-B-C). We used a frequentist approach and provide a point estimate from the network along with 95% CI, from the frequency distribution of

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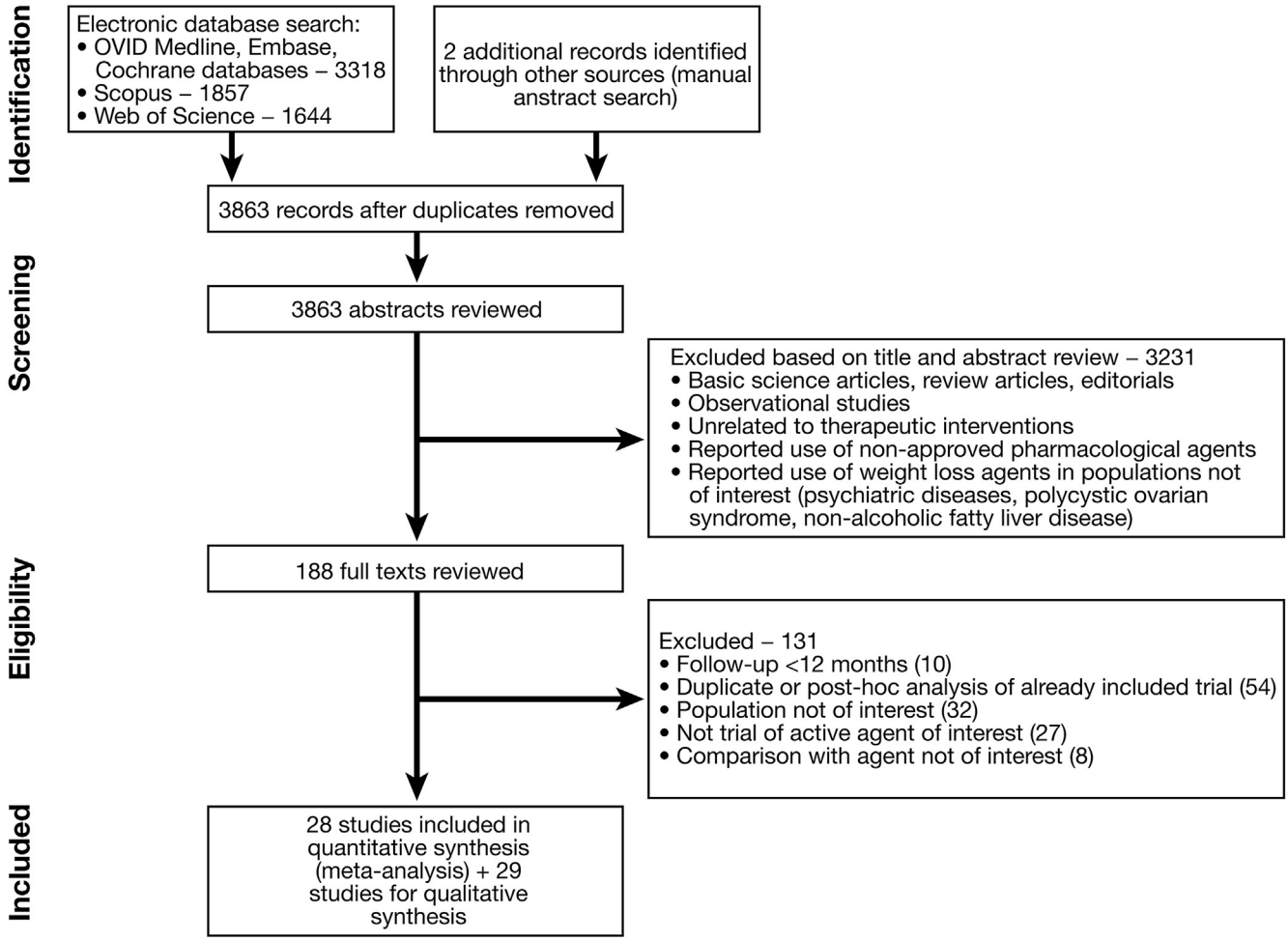


Figure 1. Study selection flowsheet.

the estimate. Comparisons were reported as both WMD and SMD along with their respective 95% CI.

We performed additional sensitivity analyses. First, to account for the effect of study-level differences in baseline risk factor on observed heterogeneity in the overall comparison, we performed random effects meta-regression analyses using the Knapp-Hartung approach for the pooled effect of pharmacologic therapies on our study outcomes, and obtained measures of residual heterogeneity (residual I^2) after adjusting for specific active agent, mean patient age, proportion of women, and mean values of baseline FBG, systolic BP, low-density lipoprotein, and BMI across studies. Second, to limit the potential difference in cardiometabolic risk factors in studies where a large proportion of patients had diabetes at study entry, we performed a network meta-analysis after excluding studies in which >10% participants had diabetes. All analyses were performed using STATA, version 14 (StataCorp, College Station, TX), and level of significance was set at an α of .05.

Quality of Evidence and Clinical Relevance

We used the using GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to rate the quality of evidence for estimates derived from direct meta-analysis. In this approach, direct evidence from RCTs starts at high quality and can be downgraded based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity, I^2 >70%), and/or publication bias to levels of moderate-, low-, and very low-quality.

Because a minimal clinically important difference has not been well-defined for these cardiometabolic risk factors, we assessed clinical relevance of observed effects based on SMD, with SMD <0.2 suggesting a minimal benefit, 0.2−0.4 suggesting modest benefit, 0.4−0.7 suggesting moderate, and >0.7 suggesting a large benefit of interventions on corresponding cardiometabolic risk factor.[13]

Funding Source

There was no funding source for this study. The corresponding author had full access to all data and was responsible for the decision to submit for publication.

Results

Study Characteristics

We identified 28 RCTs of FDA-approved weight-loss medications with 29,018 subjects who met current guidelines for long-term pharmacologic therapy for obesity, either with a BMI ≥30 kg/m^2 alone or BMI ≥27 kg/m^2 with ≥1 excess weight-related comorbidities (Supplementary Table 1).[14–41] The network of included studies is shown in

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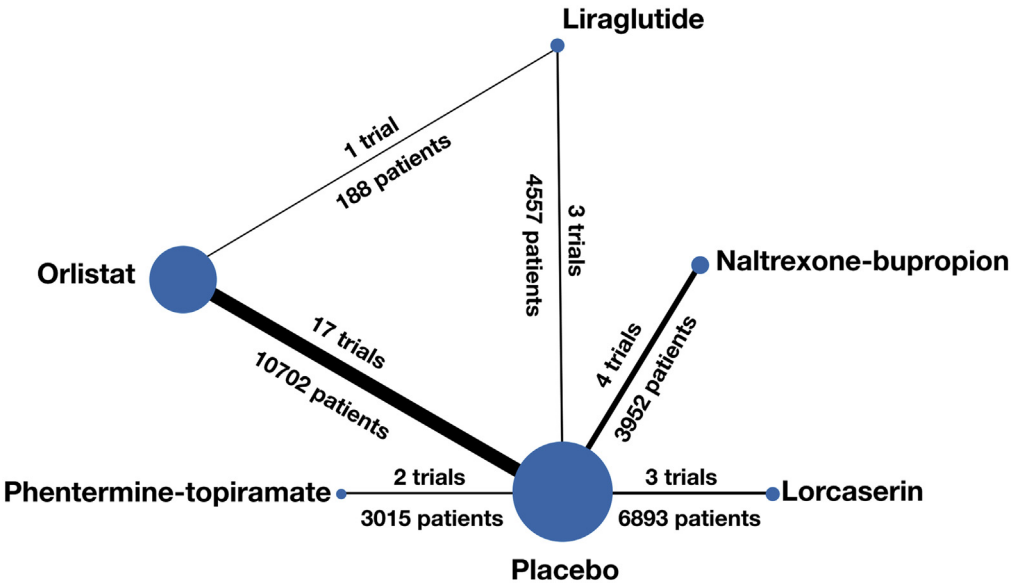


Figure 2. Network of included studies (across outcomes). Outcomes reported in each study are included in Table 1.

Figure 2. The median age of study participants across studies was 46 years (range, 41−60 years) and 77% (range, 45%−90%) were women. The median baseline BMI was 36.1 kg/m^2 (range, 32.7−42.0 kg/m^2). The baseline cardiometabolic risk profile across studies is summarized in Table 1. The baseline median FBG was 105.6 mg/dL (interquartile range [IQR], 94.6–161.5 mg/dL) and hemoglobin A1c was 7.9% (IQR, 5.7%–8.1%); 8 trials were conducted exclusively in patients with diabetes.[18,21,26,28–30,33,34] The median baseline LDL cholesterol was 122.7 mg/dL (IQR, 112.9–137.2 mg/dL) and HDL cholesterol was 46.4 mg/dL (IQR, 45.5–51.3 mg/dL); median of 34.5% (IQR, 10.3%–52.5%) of participants had dyslipidemia. Median average systolic BP was 127.5 mm Hg (IQR, 121.9–135.8 mm Hg) and diastolic BP was 79.1 mm Hg (IQR, 77.5–84.2 mm Hg) at baseline; median of 23% (IQR, 17%–36%) of participants had hypertension at baseline. WC was 110 cm (IQR, 109–115 cm) at baseline. Additionally, 18 trials with short-term follow-up (13 orlistat, 3 phentermine/topiramate, 1 liraglutide, and 1 naltrexone/bupropion) (Supplementary Table 2) and 6 multi-arm trials comparing weight-loss agents to other commonly used medications for cardiometabolic risk modification were excluded (Supplementary Table 3).

Effects on Blood Glucose Profile

Overall, for the glucose profile outcome, obesity pharmacotherapy was associated with a modest reduction in blood glucose of 4.0 mg/dL (95% CI, −4.4 to −3.6 mg/dL; SMD, −0.27 mg/dL), over placebo (Figure 3). Considerable heterogeneity was seen across agents (Supplementary Figure 1). On agent-specific comparisons using network meta-analysis, compared to placebo, liraglutide was associated with a moderate reduction in FBG of 15.6 mg/dL (95% CI, −23.7 to −7.6 mg/dL; SMD, −0.72 mg/dL) followed by orlistat (WMD, −8.0 mg/dL; 95% CI, −12.2 to −3.7 mg/dL; SMD, −0.23 mg/dL) (Figure 4*A*). None of the other agents was associated with a significant decline in FBG. Similar effects were seen for hemoglobin A1c (Supplementary Figure 2), with the moderate reduction observed with liraglutide (WMD, −0.5%; 95% CI, −0.9% to −0.2%; SMD, −0.54%) followed by orlistat (WMD, −0.4%; 95% CI, −0.6% to −0.2%; SMD, −0.38%), and no significant differences observed with other agents. On comparison of active agents, liraglutide was superior to all other agents in lowering FBG, although it only reached statistical significance compared to naltrexone-bupropion (Supplementary Table 4).

Effects on Cholesterol Profile

Pharmacotherapy for obesity had minimal effect on cholesterol profile, with very small reduction in LDL cholesterol (WMD, −0.1 mg/dL; 95% CI, −0.19 to −0.01 mg/dL; SMD, −0.14 mg/dL), and a marginal increase in HDL-cholesterol (WMD, 0.1 mg/dL; 95% CI, 0.07 to 0.13 mg/dL; SMD, 0.07 mg/dL) (Figure 3). Considerable heterogeneity was seen across agents (Supplementary Figures 3 and 4). On agent-specific comparisons using network meta-analysis, compared to placebo, orlistat was associated with a clinically significant reduction in LDL cholesterol, with a mean of −8.7 mg/dL (95% CI, −10.7 to −6.7 mg/dL; SMD, −0.27 mg/dL); phentermine-topiramate was also associated with a significant reduction in LDL cholesterol (WMD, −4.2 mg/dL; 95% CI, −8.2 to −0.2 mg/dL), though the effect size was minimal (SMD, −0.15) (Figure 4*B*). On comparison of active agents, orlistat was superior to all other agents in lowering LDL cholesterol, though this effect was only clinically meaningful in comparison to lorcaserin (SMD, −0.22 mg/dL) (Supplementary Table 5). On examining change in HDL cholesterol as an outcome, compared to placebo, naltrexone-bupropion (WMD, 2.5 mg/dL; 95% CI, 1.2 to 3.8 mg/dL; SMD, 0.40 mg/dL) and phentermine-topiramate (WMD, 2.2 mg/dL; 95% CI, 0.4 to 4.0 mg/dL; SMD, 0.19 mg/dL) were associated with increase in HDL cholesterol at 1 year (Figure 4*B*). In contrast, orlistat was associated

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Table 1. Baseline Cardiometabolic Profile of Study Participants in Randomized Clinical Trials for Weight-Loss Therapies

Study, first author, year	Intervention, n	Control, n	DM, n (%)	Hypertension, n (%)	Dyslipidemia, n (%)	SBP, *mm Hg*, mean (SD)	DBP, *mmHg*, mean (SD)	A1c, %, mean (SD)	BG, *mg/dL*, mean (SD)	LDL, *mg/dL*, mean (SD)	HDL, *mg/dL*, mean (SD)	WC, *cm*, mean (SD)
Orlistat vs placebo												
Astrup, 2012[16]	95	98	I: 3 (3) C: 4 (4)	I: 16 (17) C: 27 (28)	I: 2 (2) C: 4 (4)	I: 123 (13.5) C: 124 (11.1)	I: 76.9 (7.9) C: 76.8 (8.5)	NR	NR	I: 136.1 (29.8) C: 136.5 (34.4)	I: 51.0 (12.0) C: 49.1 (10.4)	NR
Swinburn, 2005[39]	170	169	I: 14 (8.2) C: 14 (8.3)	I: 26 (15.3) C: 31 (18.3)	I: 51 (30) C: 49 (29)	I: 137.3 (15.7) C: 136 (15.2)	I: 84 (9.9) C: 84.5 (9)	NR	I: 119.9 (47.2) C: 113.2 (32)	I: 138.4 (38.3) C: 134.2 (32.5)	I: 44.9 (10.8) C: 44.1 (12.8)	I: 112.4 (12.8) C: 114.8 (13.1)
Berne, 2005[18]	111	109	I: 111 (100) C: 109 (100)	NR	NR	I: 145 (18.2) C: 145 (16.1)	I: 84.5 (9.7) C: 84.3 (10.0)	I: 7.6 (0.8) C: 7.6 (0.8)	I: 201.6 (46.8) C:196.2 (45.0)	I: 119.9 (38.7) C: 116 (30.9)	I: 50.3 (11.6) C: 46.4 (7.7)	I: 108 (9) C: 109 (9.3)
Torgerson, 2004 (XENDOS)[40]	1650	1655	I: 0 (0) C: 0 (0)	NR	NR	C: 130.8 (15.8) I: 130.4 (15.4)	I: 82.0 (10.0) C: 82.3 (10.0)		I: 82.8 (10.8) C: 82.8 (10.8)	I: 143.1 (34.8) C: 146.9 (34.8)	I: 46.4 (11.6) C: 46.4 (11.6)	I: 115 (10.4) C: 115.4 (10.4)
Krempf, 2003[31]	346	350	I: 0 (0) C: 0 (0)	NR	NR	NR	NR	NR	NR	NR	NR	I: 105.6 (0.8) C: 106.5 (0.8)
Miles, 2002[33]	255	261	I: 255 (100) C: 261 (100)	NR	NR	I: 132.7 (0.9) C: 132.1 (0.9)	NR	I: 8.87 (0.07) C: 8.79 (0.07)	I: 208.8 (3.6) C: 199.8 (3.6)	I: 121.4 (2.3) C: 124.9 (2.3)	I: 37.9 (0.8) C: 37.9 (0.8)	NR
Hanefeld, 2002[26]	195	188	I: 195 (100) C: 188 (100)	NR	NR	I: 148 (20.4) C: 147.9 (17.8)	I: 87.0 (10.8) C: 87.2 (10.7)	I: 8.6 (1.1) C: 8.6 (1.2)	I: 197.1 (52.7) C: 197.1 (57.1)	I: 135.3 (34.8) C: 139.2 (38.7)	I: 46.4 (11.6) C:46.4 (11.6)	I: 112.4 (12.5) C: 112.0 (12.7)
Broom, 2002[19]	265	266	—	I: 54 (20.4) C: 59 (22.2)	I: 114 (43) C: 120 (45.1)	I: 141.1 (15) C: 139.2 (15.7)	I: 89 (9.7) C: 88.1 (10.1)	NR	NR	I: 146.9 (34.8) C: 146.9 (34.8)	I: 54.1 (15.5) C: 54.1 (11.6)	I: 107.8 (15.6) C: 108.6 (16.4)
Bakris, 2002[17]	278	276	I: 23 (8) C: 22 (8)	I: 278 (100) C: 276 (100)	—	I: 154.2 (13.4) C: 150.8 (12.7)	I: 98.4 (37) C: 98.3 (35)	NR	NR	I: 139.2 (34.8) C:139.2 (38.7)	I: 46.4 (15.5) C: 46.4 (11.6)	I: 108.6 (12.2) C: 110.8 (12.5)
Kelley, 2002[30]	274	276	I: 274 (100) C: 276 (100)	NR	NR	I: 135.1 (0.9) C: 134.9 (0.9)	I: 79.5 (0.5) C: 80.9 (0.6)	I: 9.01 (0.07) C: 8.99 (0.07)	I: 196.4 (3.6) C: 200.9 (3.6)	I: 130.3 (2.3) C: 127.6 (2.3)	I: 41.4 (0.8) C: 41.4 (0.8)	NR
Rossner, 2000[36]	244	243	NR	NR	I: 20 (8.3) C: 24 (10.1)	I: 125.5 (14.9) C: 127.3 (16.1)	I: 79.5 (9.4) C: 81.2 (9.8)	NR	I: 98.5 (12.2) C: 100.1 (17.6)	I: 133 (33.3) C: 137.3 (37.9)	I: 45.2 (11.6) C: 45.2 (13.9)	NR
Lindgarde, 2000[32]	190	186	I: 17 (8.9) C: 13 (7)	I: 74 (38.9) C: 81 (43.8)	I: 75 (39) C: 75 (40)	I: 146 (19) C: 145 (17)	I: 87 (10) C: 88 (10)	I: 5.7 (1.2) C: 5.5 (0.9)	I: 119.2 (45.5) C: 114.3 (35.3)	I: 145.0 (53.4) C: 141.5 (54.5)		I: 106 (10.8) C: 106 (11)
Hauptman, 2000[27]	210	212	NR	NR	NR	I: 120 (1) C: 121 (1)	I: 78 (1) C: 78 (1)	NR	I: 101.9 (0.7) C: 101.9 (0.7)	I: 122.2 (2.3) C: 122.2 (1.9)	I: 46.4 (0.8) C: 45.2 (0.8)	NR
Finer, 2000[23]	114	114	I: 0 (0) C: 0 (0)	I: 6 (5.5) C: 2 (2)	I: 59 (52) C: 60 (53)	NR	NR	NR	NR	I: 141.9 (32.5) C: 141.9 (32.9)	I: 47.2 (10.8) C: 47.2 (11.2)	NR
Davidson, 1999[20]	668	224	I: 26 (4) C: 10 (4.5)	I: 54 (8.2) C: 20 (9)	I: 69 (10.5) C: 12 (5.4)	NR	NR	NR	I: 101.2 (0.5) C: 100.8 (0.5)	I: 142.7 (2.3) C: 123 (1.9)	I: 45.2 (0.8) C: 46.8 (0.8)	NR
Sjostrom, 1998[37]	345	343	NR	NR	NR	I: 129 (0.60) C: 128 (0.60)	82.4 (0.4) 81.9 (0.4)	NR	I: 105.1 (0.5) C: 104.9 (0.5)	I: 137.3 (1.2) C: 37.3 (1.2)	I: 44.5 (0.4) C: 44.9 (0.4)	I: 105.4 C: 105.9
Hollander, 1998[28]	162	159	I: 162 (100) C: 159 (100)	NR	NR	NR	NR	I: 8.05 (0.98) C: 8.2 (1.07)	I: 159.3 (30.2) C: 163.6 (33.7)	NR	NR	NR
Loracaserin vs placebo												
O'Neil, 2012 (BLOOM-DM)[34]	256	252	I: 256 (100) C: 252 (100)	NR	NR	I: 126.6 (12.7) C: 126.5 (13.5)	I: 77.9 (8.0) C: 78.7 (7.9)	I: 8.1 (0.8) C: 8.1 (0.8)	I: 164.5 (48.1) C: 159.7 (41.7)	I: 95.0 (30.4) C: 94.6 (30.2)	I: 45.3 (11.0) C: 45.7 (12.7)	I: 115.8 (11.8) C: 113.5 (12.6)
Fidler, 2011 (BLOSSOM)[22]	1602	1601	NR	I: 388 (24.2) C: 382 (23.9)	I: 455 (28.4) C: 438 (27.4)	I: 122.1 (12.2) C: 121.9 (11.9)	I: 78.1 (8.1) C: 78.3 (8.1)	I: 5.6 (0.4) C: 5.6 (0.4)	NR	I: 116.7 (32.1) C: 113.9 (28.6)	I: 51.8 (13.3) C: 51.4 (13.2)	I: 109.2 (12.4) C: 110.9 (12.9)
Smith, 2010 (BLOOM)[38]	1595	1587	I: 0 (0) C: 0 (0)	NR	NR	I: 120.7 (0.3) C: 121.1 (0.3)	I: 76.8 (0.2) C: 77.1 (0.2)	I: 5.7 (0.0) C: 5.7 (0.0)	I: 94.3 (0.3) C: 94.1 (0.3)	I: 112.1 (0.8) C: 113.8 (0.8)	I: 54.7 (0.3) C: 55.4 (0.4)	I: 109.6 (0.3) C: 109.2 (0.3)

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Table 1. Continued

Study, first author, year	Intervention, n	Control, n	DM, n (%)	Hypertension, n (%)	Dyslipidemia, n (%)	SBP, *mm Hg*, mean (SD)	DBP, *mmHg*, mean (SD)	A1c, %, mean (SD)	BG, *mg/dL*, mean (SD)	LDL, *mg/dL*, mean (SD)	HDL, *mg/dL*, mean (SD)	WC, *cm*, mean (SD)
Naltrexone-bupropion vs placebo												
Apovian, 2013 (COR II)[15]	1001	495	I: 0 (0) C: 0 (0)	I: 212 (21.2) C:106 (21.4)	I: 560 (55.9) C: 263 (53.1)	I: 118.1 (10); C: 118.2 (10.5)	I: 76.8 (7); C: 76.8 (7)	NR	I: 94.8 (11.2); C: 94.2 (10.4)	I: 119.8 (30.2) C:117.1 (32.6)	I: 51.4 (13.3); C: 51.4 (13.1)	I: 109.3 (11.9) C: 108.9 (11.7)
Hollander, 2013 (COR-DM)[29]	333	169	I: 333 (100) C: 169 (100)	NR	I: 280 (83.6) C: 145 (85.3)	I: 125 (11); C: 124.5 (11.6)	I: 77.5 (7.5); C: 77.4 (7.4)	I: 8.0 (0.8); C: 8.0 (0.9)	I: 160.3 (40.3); C: 163.9 (44.5)	I: 100.2 (34.2) C: 101 (33.9)	I: 46.2 (10.2); C: 46.1 (11.5)	I: 115.6 (12.6); C: 114.3 (12.4)
Wadden, 2011 (COR-BMOD)[41]	591	202	I: 0 (0) C: 0 (0)	NR	NR	I: 116.6 (10.1); C: 116.7 (10.9)	I: 78.3 (7.0); C: 77.1 (7.4)	NR	I: 92.4 (10.7) C: 94.1 (20.1)	I: 109.5 (27.5); C: 109.2 (27.3)	I: 53.6 (13.5); C: 55.3 (12.9)	I: 109.3 (11.4) C: 109 (11.8)
Greenway, 2010 (COR I)[25]	583	581	I: 0 (0) C: 0 (0)	I: 130 (22) C: 113 (19)	I: 284 (49) C: 288 (50)	I: 118.9 (9.9); C: 119 (9.8)	I: 77.1 (7.2); C: 77.3 (6.6)	NR	I: 94.2 (12.1); C: 93.9 (11.2)	I: 119.1 (32.5) C: 119.9 (34.8)	I: 51.8 (13.5); C: 52.2 (13.5)	I: 108.8 (11.3) C: 110 (12.2)
Phentermine-topiramate vs placebo												
Allison 2012 (EQUIP)[14]	512	514	I: 0 (0) C: 0 (0)	NR	NR	I: 122.0 (11.6) C: 121.8 (11.4)	I: 77.4 (7.7) C: 77.2 (7.8)	NR	I: 93.0 (9.5) C: 93.0 (8.7)	I: 119.8 (30.1) C: 121.3 (32.0)	I: 49.8 (11.7) C: 49.5 (13.1)	I: 120.1 (14.6) C: 120.5 (13.9)
Gadde, 2011 (CONQUER)[24]	995	994	I: 664 (67) C: 675 (68)	I: 363 (36) C: 354 (36)	NR	I: 127.9 (13.4) C: 128.9 (13.5)	I: 80.1 (9.1) C: 81.1 (9.2)	I: 5.9 (0.8) C: 5.9 (0.8)	I: 106.2 (21.6) C: 106.2 (23.4)	I: 123.7 (34.8) C: 123.7 (34.8)	I: 50.3 (15.5) C: 50.3 (15.5)	I: 113.2 (12.2) C: 113.4 (12.2)
Liraglutide vs Placebo												
Davies, 2015 (SCALE-DM)[21]	423	212	I: 423 (100) C: 212 (100)	I: 293 (69.3) C: 145 (68.4)	I: 295 (69.7) C: 126 (59.4)	I: 128.9 (13.6) C: 129.2 (13.6)	I: 79.0 (8.6) C: 79.3 (9.5)	I: 7.9 (0.8) C: 7.9 (0.8)	I: 158.4 (32.8) C: 155.5 (33.0)	I: 86.4 (35.5) C: 85.2 (39.3)	I: 45.2 (25.0) C: 45.4 (24.8)	I: 118.0 (14.4) C: 117.3 (14.0)
Pi-Sunyer, 2015 (SCALE Obesity)[35]	2487	1244	I: 0 (0) C: 0 (0)	I: 850 (34.2) C: 446 (35.9)	I: 737 (29.6) C: 359 (28.9)	I: 123.0 (12.9) C: 123.2 (12.8)	I: 78.7 (8.6) C: 78.9 (8.5)	I: 5.6 (0.4) C: 5.6 (0.4)	I: 95.9 (10.6) C: 95.5 (9.8)	I: 111.6 (27.9) C: 112.2 (27.6)	I: 51.4 (26.2) C: 51.0 (26.4)	I: 115.0 (14.4) C: 114.5 (14.3)
Astrup, 2012[16]	93	98	I: 4 (4) C: 4 (4)	I: 11 (12) C: 27 (28)	I: 7 (8) C: 4 (4)	I: 124 (11.3) C: 124 (11.1)	I: 77.8 (8.3) C: 76.8 (8.5)	NR	NR	I: 131.5 (30.2) C: 136.5 (34.4)	I: 49.5 (12.4) C: 49.1 (10.4)	NR
Liraglutide vs orlistat												
Astrup, 2012[16]	93	95	I: 4 (4) C: 3 (3)	I: 11 (12) C: 16 (17)	I: 7 (8) C: 2 (2)	I: 124 (11.3) C: 123 (13.5)	I: 77.8 (8.3) C: 76.9 (7.9)	NR	NR	I: 131.5 (30.2) C: 136.1 (29.8)	I: 49.5 (12.4) C: 51.0 (12.0)	NR

A1c, glycated hemoglobin; BG, blood glucose; C, control; DBP, diastolic blood pressure; DM, diabetes mellitus; I, intervention; NR, not reported; SBP, systolic blood pressure.

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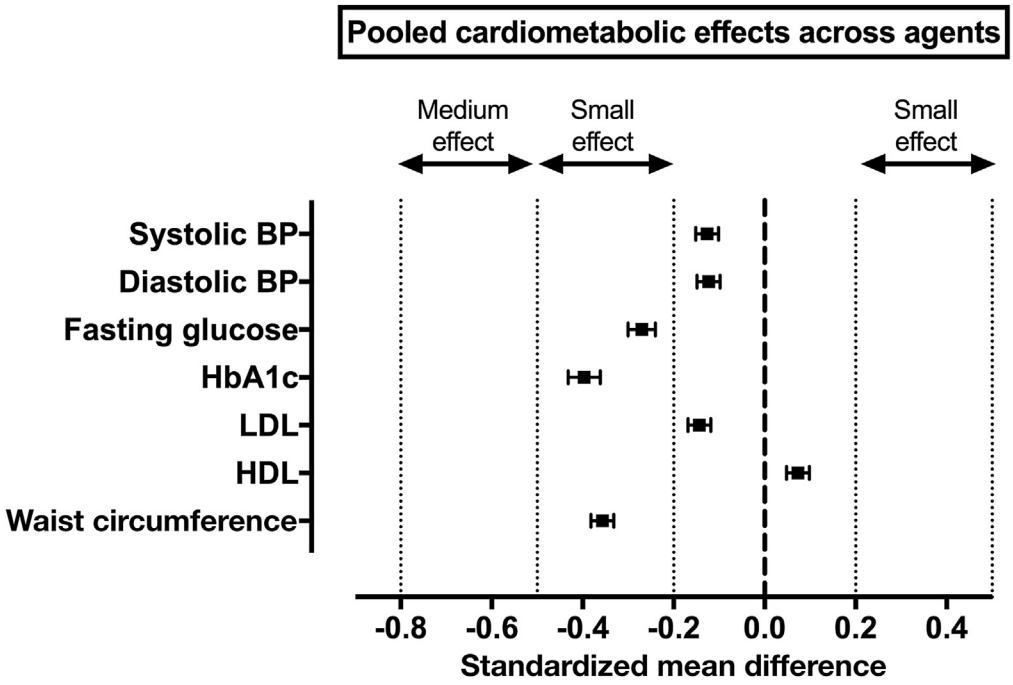


Figure 3. Pooled effect of any pharmacologic therapy for obesity compared to placebo on each study outcome reported as SMDs.

with decline in HDL cholesterol (WMD, −1.1 mg/dL; 95% CI, −1.9 to −0.4 mg/dL; SMD, −0.11 mg/dL) compared to placebo. On comparison of active agents, no agent was clearly superior to others in improving HDL-cholesterol; in contrast, orlistat was inferior to all other agents (Supplementary Table 5).

Effects on Blood Pressure

Pharmacotherapy had minimal effect on BP, with very small decline in systolic (WMD, −1.8 mm Hg; 95% CI, −2.0 to −1.6 mm Hg; SMD, −0.13 mm Hg), and diastolic BP (WMD, −2.0 mm Hg; 95% CI, −2.0 to −1.9 mm Hg; SMD, −0.12 mm Hg) (Figure 3). Considerable heterogeneity was seen across agents (Supplementary Figures 5 and 6). On agent-specific comparisons, using network meta-analysis, compared to placebo, phentermine-topiramate, liraglutide, and orlistat were associated with modest reductions in systolic BP of 3.7 mm Hg (95% CI, −5.6 to −1.9 mm Hg; SMD, −0.23 mm Hg), 2.8 mm Hg (95% CI, −4.3 to −1.2 mm Hg; SMD, −0.24 mm Hg) and 1.7 mm Hg (95% CI, −2.4 to −0.9 mm Hg; SMD, −0.19 mm Hg), respectively (Figure 4*C*). Similar changes were seen in diastolic BP (Figure 4*C*). On comparison of active agents, phentermine-topiramate was associated with a greater magnitude of reduction in systolic BP compared to all other active agents (range, −2.1 to −4.3 mm Hg), and a modestly greater reduction in diastolic BP compared to naltrexone-bupropion (WMD, −1.5 mm Hg; 95% CI, −2.5 to −0.4 mm Hg) (Supplementary Table 6).

Effects on Waist Circumference

Pharmacotherapy for obesity was associated with a small to moderate 3.3-cm decline in WC (95% CI, −3.5 to −3.1 cm; SMD, −0.36 cm) (Figure 3). Considerable heterogeneity was seen across agents (Supplementary Figure 7). On agent-specific comparisons, using network meta-analysis, compared to placebo, all agents were associated with a small to moderate decrease in WC: phentermine-topiramate by 7 cm (95% CI, −8.4 to −5.6 cm; SMD, −0.49 cm), liraglutide by 4 cm (95% CI, −5.0 to −3.3 cm; SMD, −0.63 cm), 3.5 cm with naltrexone-bupropion (95% CI, −4.4 to −2.6 cm; SMD, −0.37 cm), 2.5 cm with lorcaserin (95% CI, −3.3 to −1.7 cm, SMD, −0.31 cm), and 2.3 cm with orlistat (95% CI, −2.8 to −1.7 cm; SMD, −0.26 cm) (Figure 4*D*). On comparison of active agents, phentermine-topiramate was associated with higher decrease in WC compared to other agents (range, −2.9 to −4.8 cm; SMD range, −0.11 cm to −0.23 cm). Liraglutide was also associated with significantly greater decrease in WC compared to lorcaserin (WMD, −1.6 cm; 95% CI, −2.8 to −0.5 cm; SMD, −0.32 cm) and orlistat (WMD, −1.9 cm; 95% CI, −2.8 to −0.9 cm; SMD, −0.37 cm) (Supplementary Table 7).

Small Study Effects and Sensitivity Analyses

There was no evidence of small study effects on analysis of funnel plot symmetry. In sensitivity analyses, residual heterogeneity after accounting for patient characteristics in meta-regression analyses was lower (range, 44%–82%) than pairwise analyses, but was >50% for most comparisons. Notably, between-study heterogeneity was mainly driven by differences in magnitude of the effect sizes, rather than the direction of the effect. Further, in analyses excluding 9 studies in which >10% participants had diabetes, we observed similar findings to our primary analyses (data not shown).

Quality of Evidence

GRADE quality of evidence summary and its clinical relevance is summarized in Figure 3 and

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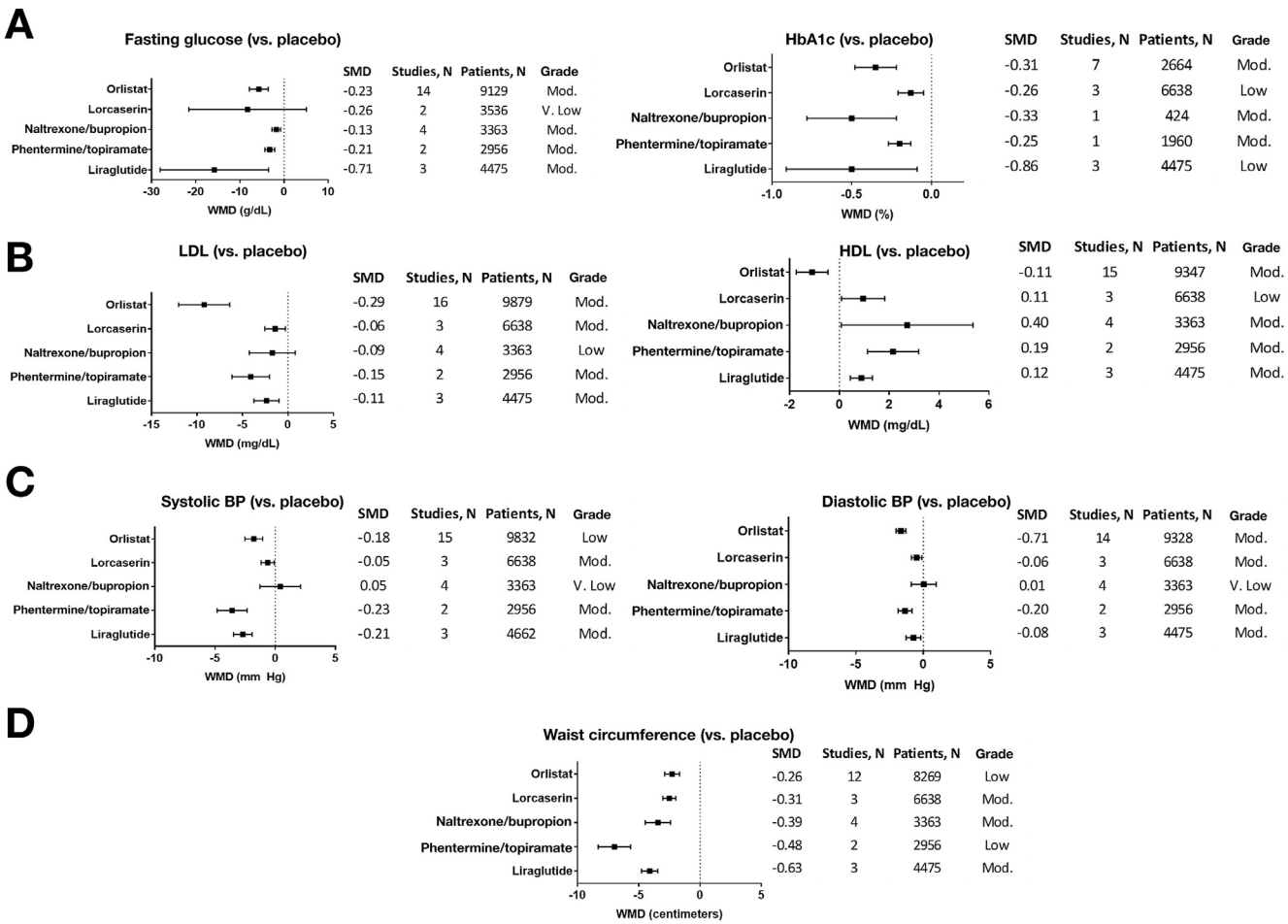


Figure 4. Impact of individual agents against placebo after 1 year of treatment on (*A*) measures of blood glucose control: FBG and hemoglobin A1c, (*B*) measures of cholesterol metabolism: LDL and HDL, (*C*) blood pressure, and (*D*) WC.

Supplementary Table 8. Due to high attrition rates for all trials (30%−45%), evidence was rated down for risk of bias. Overall, there was moderate certainty suggesting a moderate to large benefit of liraglutide on glucose profile and WC, and moderate certainty suggesting a moderate benefit with naltrexone-bupropion on increasing HDL cholesterol. For most other agents and outcomes, there was generally low to moderate certainty suggesting either a minimal or modest benefit of weight-loss medications on cardiometabolic risk profile.

Discussion

Although FDA-approved pharmacologic agents for long-term treatment of obesity result in significant weight loss, with 20%−54% patients achieving ≥10% weight loss,[3] they appear to have modest impact on modifying key cardiometabolic risk factors, even 1 year after therapy (SMD range, 0.07−0.36). Most drugs were associated with improvements in WC, but only marginal improvements in serum cholesterol profile and BP.

The effect of individual drugs varied substantially, and closely followed their mechanism of action. Liraglutide, an anti-diabetic, was associated with moderate improvements in glucose profile and WC, with moderate confidence in estimates, with small BP-lowering and minimal effects on the cholesterol profile. Naltrexone-bupropion was associated with moderate increase in HDL cholesterol with moderate confidence in estimates, but minimal effects on LDL-cholesterol, glucose profile, and BP. Phentermine-topiramate, which induces most weight loss, was associated with largest improvement in WC, but only modest improvements in the glucose profile and BP, and had minimal effects on LDL or HDL cholesterols. Orlistat, as a lipase inhibitor, was associated with decrease in LDL cholesterol, but also lower HDL cholesterol, which may be unfavorable from a cardiometabolic risk perspective. None of the drugs consistently improved all cardiometabolic risk factors and no single pharmacologic agent was superior to others. However, there were drug-specific favorable effects on different components of the cardiometabolic risk profile.

The limited improvements in cardiometabolic risk with drug therapies that are otherwise effective at weight loss underscores the need for dedicated studies to assess the effects of these medications on meaningful changes in cardiovascular risk. Further, because there are drug-specific effects on important facets of cardiometabolic risk, an approach that accounts for a patient's baseline risk in the

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selection of drug therapies would need to be evaluated in dedicated studies.

The FDA mandates that all drugs being considered for treatment of obesity undergo long-term cardiovascular safety trials—it is crucial that these trials are designed to ensure, while assessing drug safety potential, that long-term beneficial effects on cardiovascular risk profile are examined.[42] Only 2 published trials that have specifically addressed cardiovascular risk with these agents, the LIGHT trial and the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial. The LIGHT trial was designed to assess the effect of naltrexone-bupropion on BP and heart rate, particularly given concerns regarding heart rate elevations in phase 3 trials. However, the trial was stopped prematurely due to protocol violations.[5,43] The LEADER trial examined low-dose (1.8 mg) liraglutide as a non-insulin therapy in diabetic adults with or without obesity conducted under an FDA mandate on cardiovascular safety trials for all anti-diabetic medications. In 9430 patients followed for 4 years, liraglutide was associated with a 13% lower rate of major adverse cardiovascular events compared to placebo.[4] Notably, patients in LEADER did not receive any behavioral or dietary counseling for weight loss, which are important components of all weight-loss studies.

These findings are in contrast with more substantial cardiometabolic benefits associated with certain other contemporary weight-loss therapies, particularly bariatric surgery. In both diabetic and nondiabetic obese adults, bariatric surgery is associated with robust favorable modification of cardiometabolic risk factors, as well as reduction in risk of cardiovascular events.[44–50] This likely represents a combination of greater magnitude of weight loss with bariatric surgery compared with pharmacotherapy,[51,52] and neurohormonal changes secondary to bariatric surgery,[53] such as increases in incretin or satiety hormones,[54] and improvement in biochemical, inflammatory, and oxidative profiles.[55] The impact of endoscopic bariatric and metabolic therapies on cardiometabolic risk profile remains to be seen.[56]

Our study findings should be interpreted in the light of the following limitations. First, data are derived predominantly from drug−placebo comparisons, with only 1 study comparing 2 active agents (liraglutide vs orlistat) against each other.[16] Second, while we used strict inclusion and exclusion criteria to ensure comparability across trials, we cannot exclude the possibility of conceptual heterogeneity across studies. Third, there was statistical heterogeneity in the effect size in pooled analyses across therapies. However, this was substantially lower for individual drug classes. Moreover, our sensitivity analyses suggest that some of the observed heterogeneity may be attributable to differences in baseline risk across trials. The limited reporting of co-interventions, however, limits further assessment of differences in risk-modifying therapies, such as lipid-lowering therapy across trials. Fourth, the trials had a large rate of attrition (approximately 30%). To account for missing data, we used study-reported last observed carried forward imputation values for outcomes as suggested by the FDA guidelines for obesity pharmacotherapy. Finally, most included studies did not have a follow-up beyond 1 year of drug therapy and longer studies are needed to assess the impact of adverse cardiovascular events.

In conclusion, while all currently approved pharmacologic weight-loss therapies are associated with significant weight loss, they appear to have minimal to modest effects on cardiometabolic risk profile of obese and overweight adults, even after a year of drug therapy. Further research is needed to evaluate the long-term benefit of these medications on cardiovascular risk.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.12.024.

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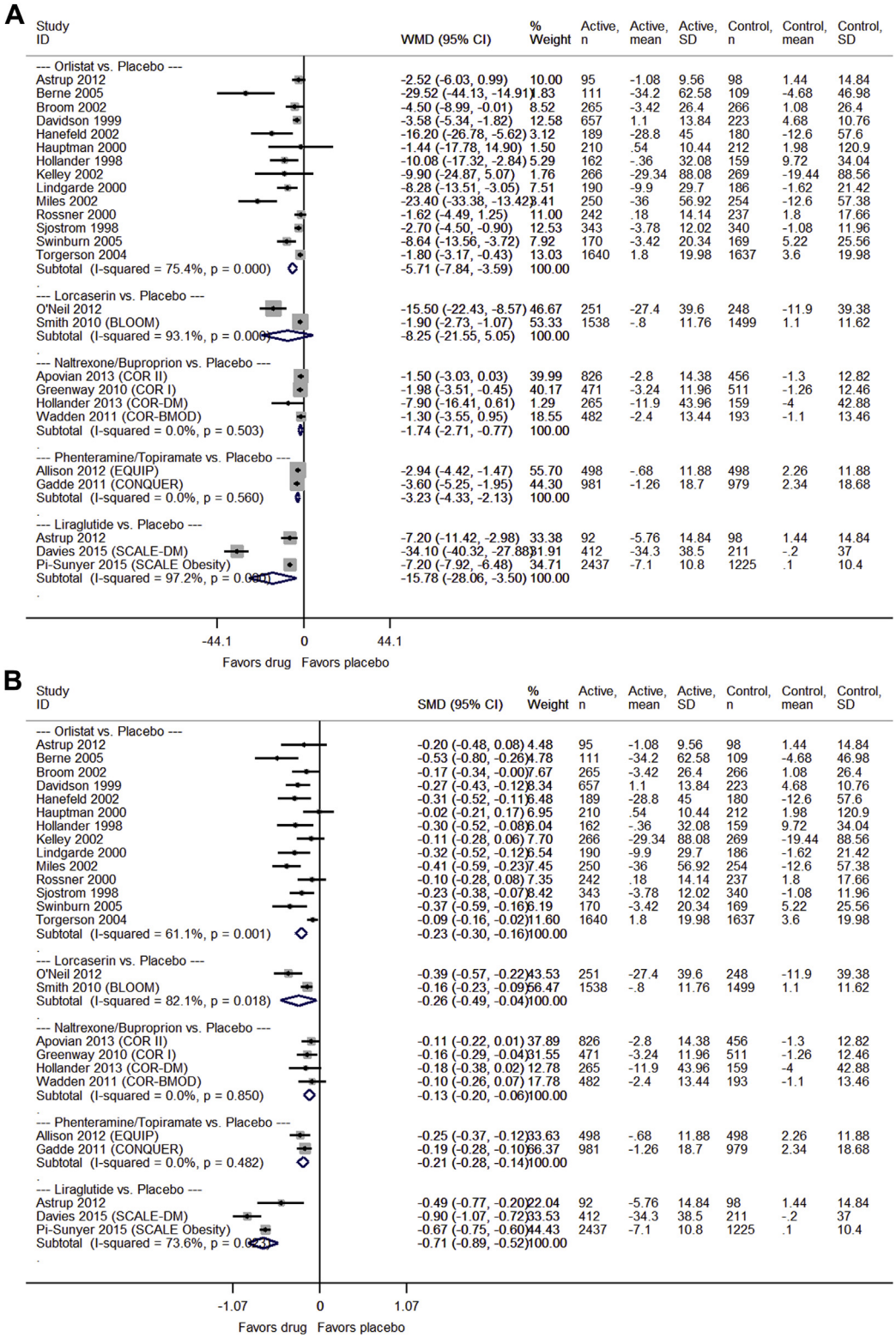
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Conflicts of interest
This author discloses the following: Dr Camilleri is funded through R56-DK67071 to study effects of liraglutide and has received supplies of liraglutide from Novo-Nordisk for this National Institutes of Health–funded research. The remaining authors disclose no conflicts.

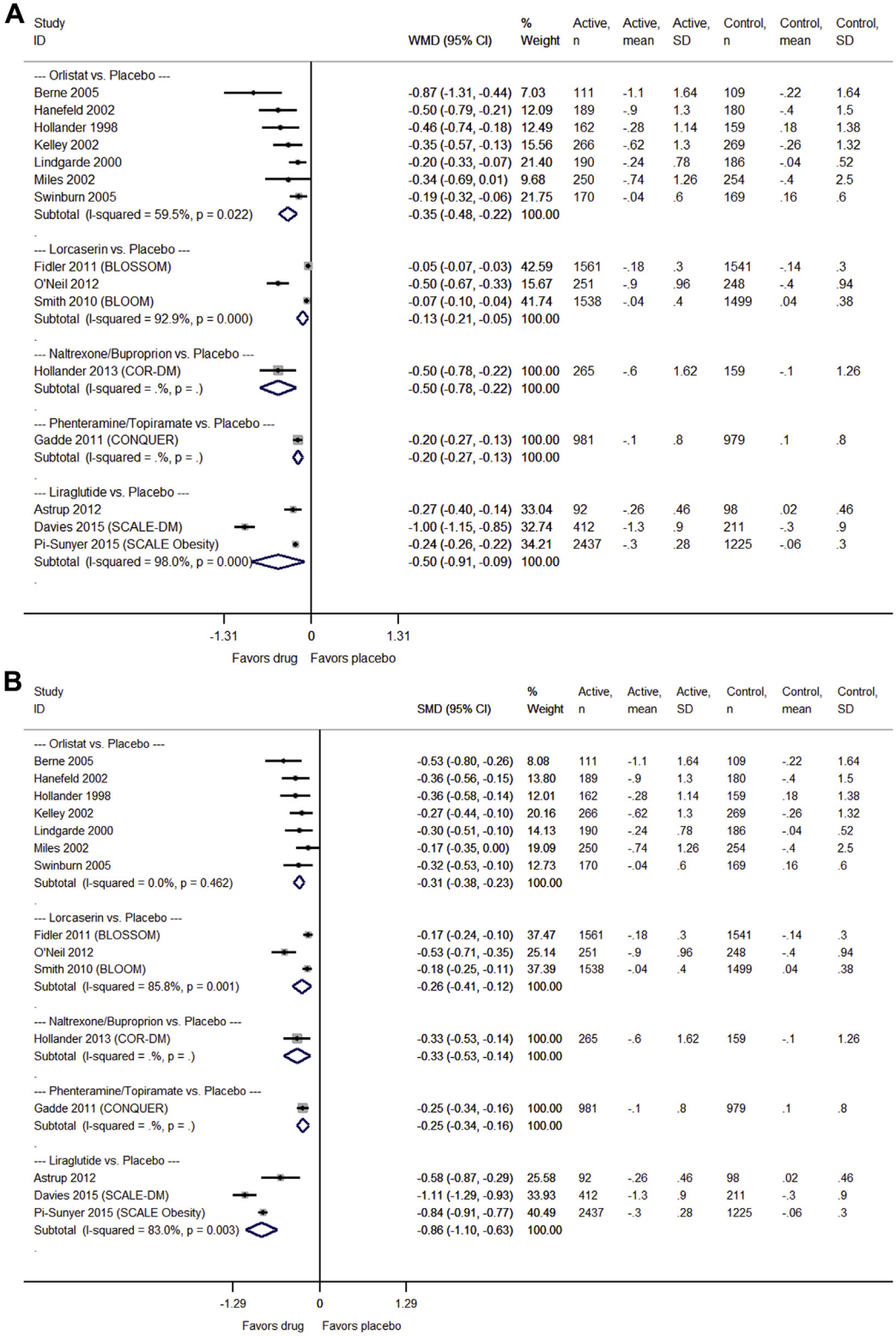
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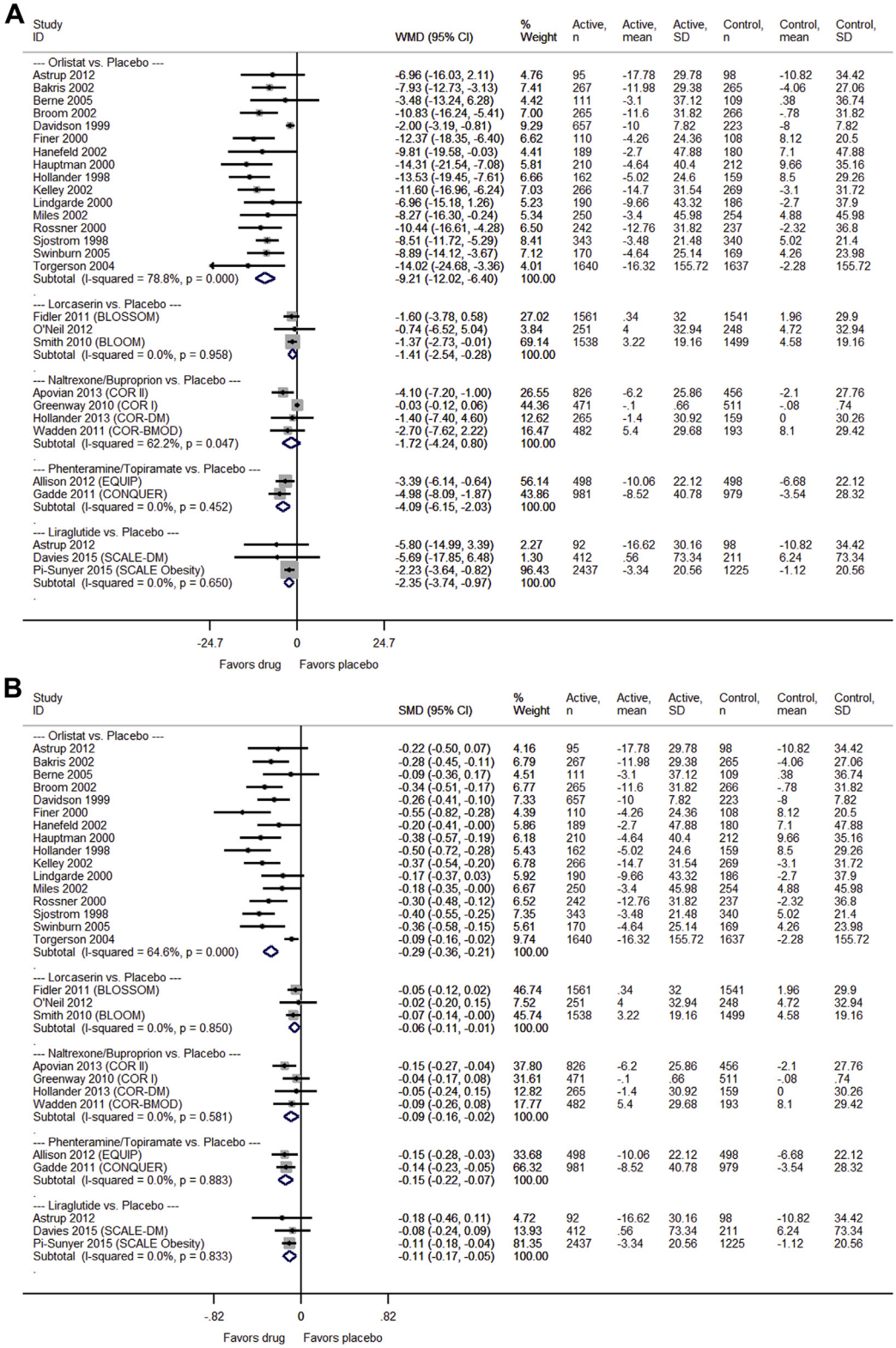
Supplementary Figure 1. Direct meta-analysis of different pharmacological interventions for fasting blood glucose, (*A*) Weighted mean difference, (*B*) Standardized mean difference.

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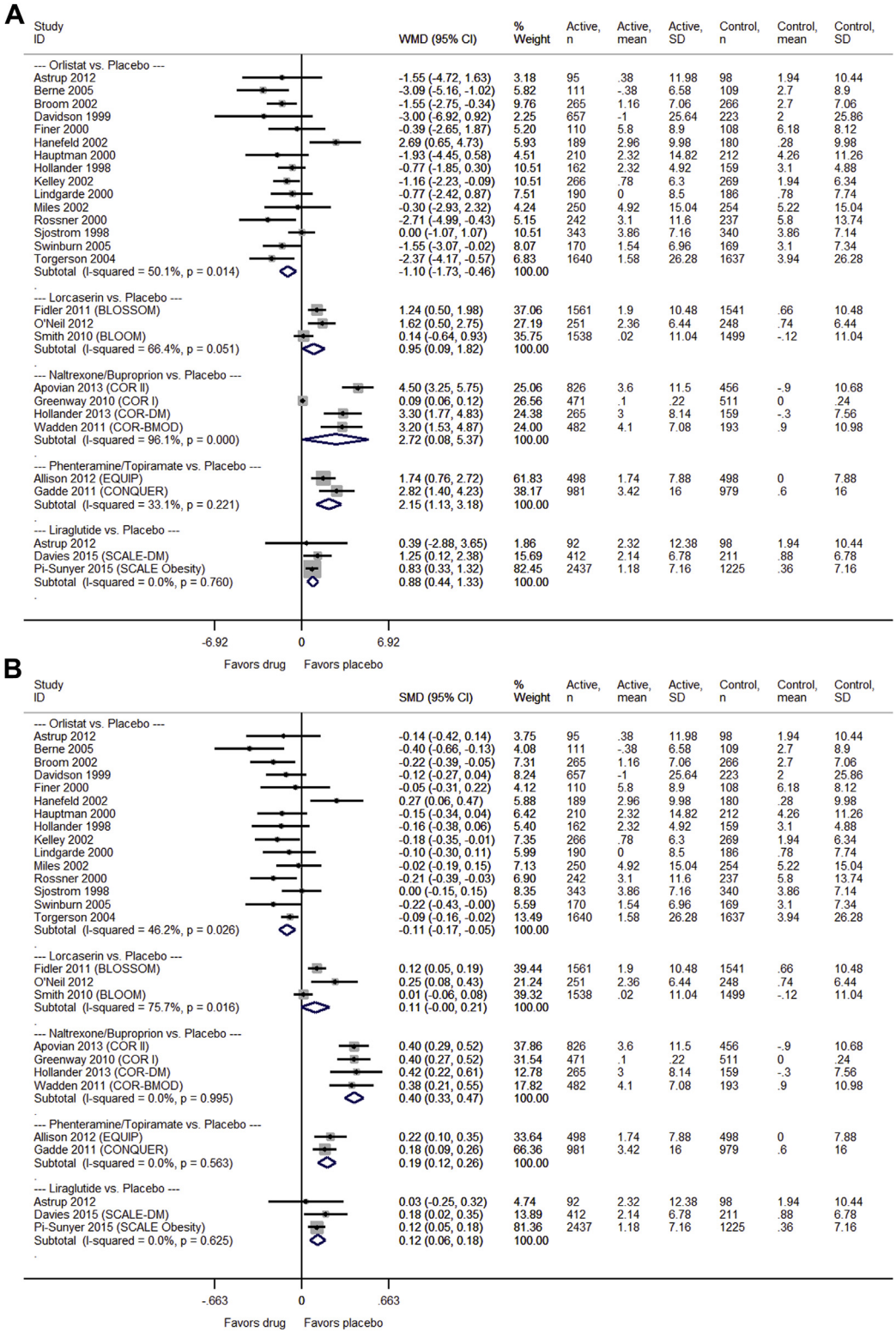
Supplementary Figure 2. Direct meta-analysis of different pharmacological interventions for hemoglobin A1c, (*A*) Weighted mean difference, (*B*) Standardized mean difference.

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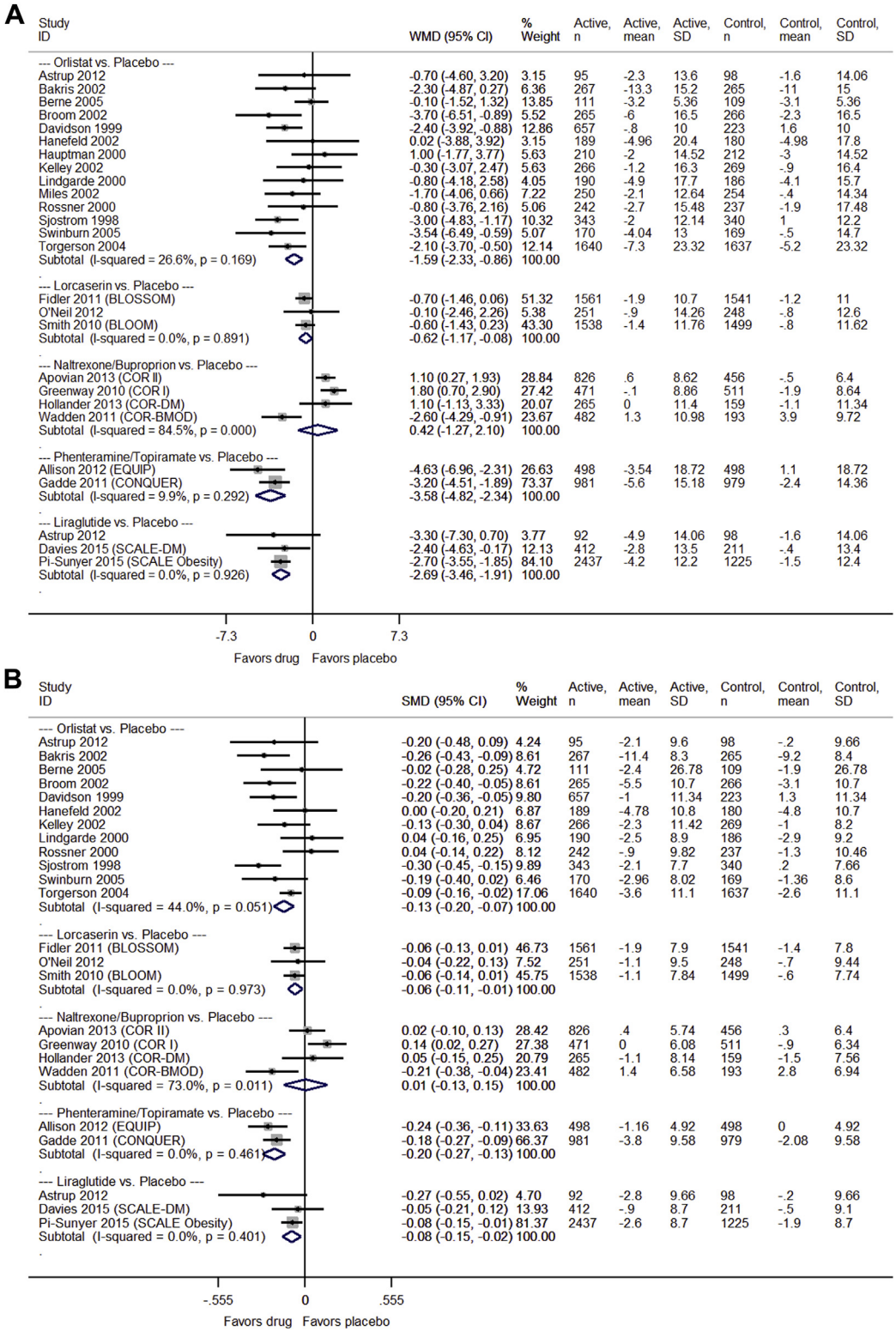
Supplementary Figure 3. Direct meta-analysis of different pharmacological interventions for LDL, (*A*) Weighted mean difference, (*B*) Standardized mean difference.

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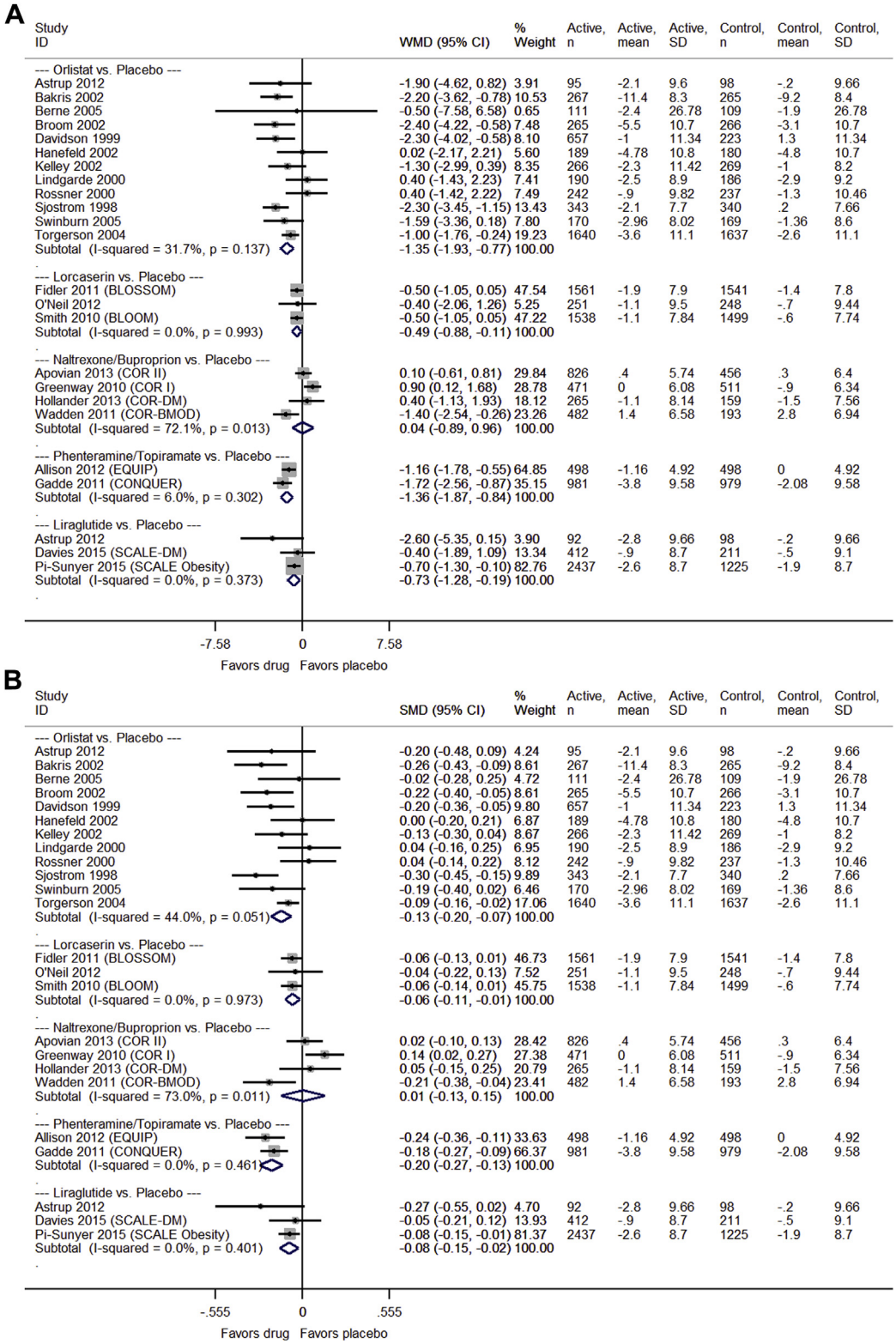
Supplementary Figure 4. Direct meta-analysis of different pharmacological interventions for HDL, (*A*) Weighted mean difference, (*B*) Standardized mean difference.

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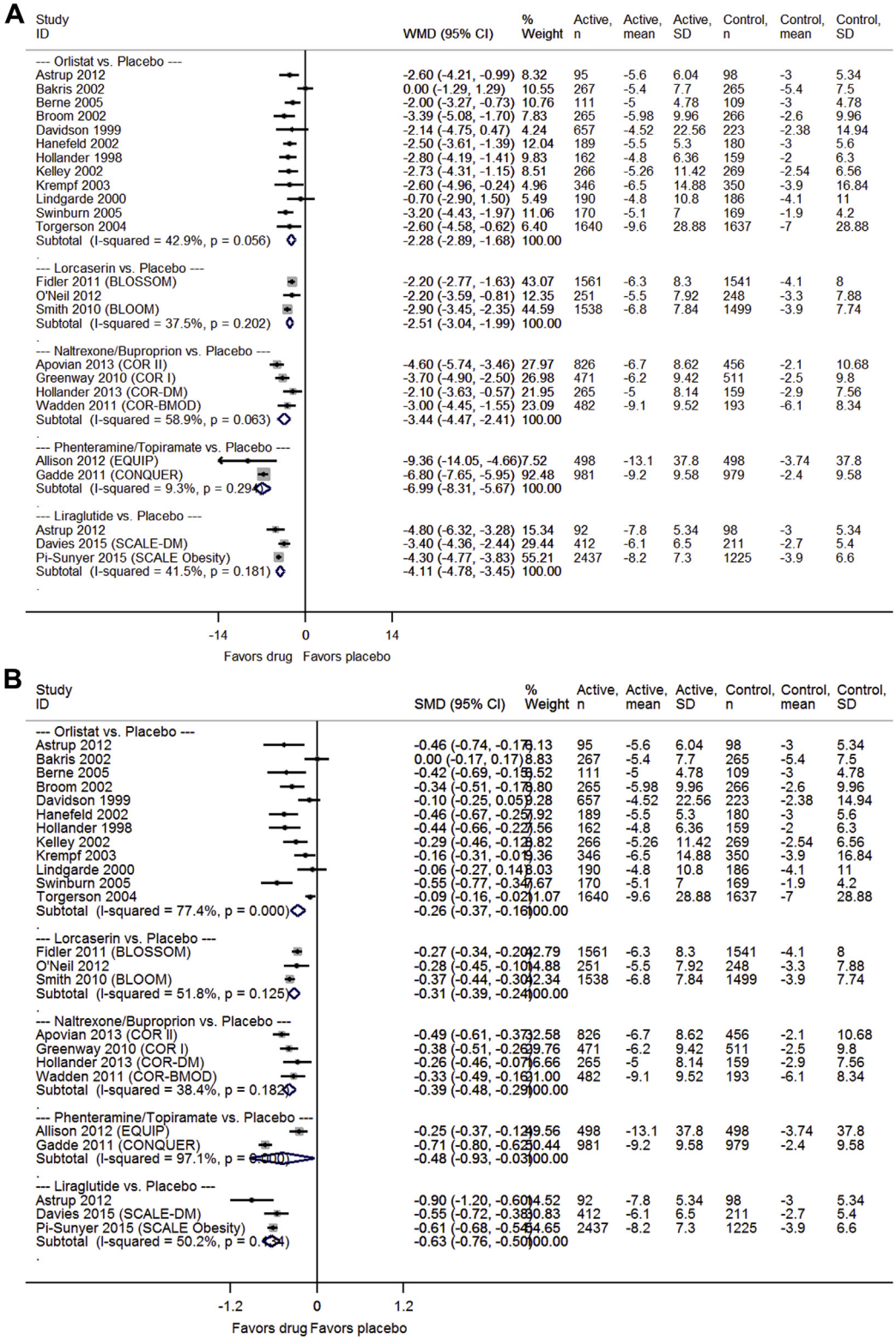
Supplementary Figure 5. Direct meta-analysis of different pharmacological interventions for systolic blood pressure, (*A*) Weighted mean difference, (*B*) Standardized mean difference.

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Supplementary Figure 6. Direct meta-analysis of different pharmacological interventions for diastolic blood pressure (*A*) Weighted mean difference, (*B*) Standardized mean difference.

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Supplementary Figure 7. Direct meta-analysis of different pharmacological interventions for waist circumference, (*A*) Weighted mean difference, (*B*) Standardized mean difference.

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